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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/770,418	LE MOUELLIC ET AL.	
	Examiner	Art Unit	
	WU-CHENG Winston SHEN	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 September 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *71-77* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *71-77* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *04 February 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination (RCE) under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 09/15/2008 has been entered.

Claim 1-70 and 78-101 are cancelled. Claims 71, 76 and 77 are amended. Claims 71-77 are pending and currently under examination

This application 10/770,418 filed on Feb. 04, 2004 is a CON of 10/639,754 08/13/2003 which is a CON of 08/466,699 06/06/1995 PAT 6,638,768, which is a CON of 08/301,037 09/06/1994 PAT 6,528,313, which is a CON of 08/048,056 04/19/1993 ABN, which is a CON of 07/598,679 12/19/1990 ABN. Relevant foreign applications are FRANCE PCT/FR90/00185 03/19/1990 and FRANCE 89 03630 filed on 03/20/1989.

Claim objection

1. Previous objection of claim 77 for lacking a period at the end of claim 77 is ***withdrawn*** because the claim has been amended.

Claim Rejection - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

2. Claims 71-77 **remain** rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicant's arguments filed 09/15/2008 have been fully considered and they are not persuasive. Previous rejection is ***maintained*** for the reasons of record advanced on pages 3-4 of the office action mailed on 03/14/2008.

(i) With regard to the aspect of the rejection pertaining to recitation of the limitation "*the* first and second endogenous sequences are *adjacent to* a desired insertion site in the genome of the mammalian cell", Applicant indicates that the amended claims 71, 76, and 77 no longer recite the limitation. Claims 72-75 depend from claim 71. This aspect of the rejection is ***withdrawn***.

(ii) With regard to the aspect of the rejection pertaining to recitation of "recombination DNA sequences", Applicant argues that claims 71, 76, and 77 have been amended to recite "wherein, the first and second recombination DNA sequences direct homologous recombination events between the first and second endogenous DNA sequences in the genome of the mammalian cell upon introduction of the DNA construct into the mammalian cell, such that the first and second insertion DNA sequences are inserted into the genome of the mammalian cell between the first and second endogenous DNA sequences". Applicant indicates that the support can be found throughout the application as filed, such as at page 4, lines 1-13.

Applicant's arguments filed 09/15/2008 have been fully considered and they are not persuasive. The Examiner notes that amended independent claims 71, 76 and 77 recite the limitation "(A) a first recombination DNA sequence and a second recombination DNA sequence, wherein the first recombination DNA sequence is homologous to a first endogenous DNA

sequence in the genome of a mammalian cell, and the second recombination DNA sequence is homologous to a second endogenous DNA sequence in the genome of the mammalian cell".

Amended independent claims 71, 76 and 77 further recite newly added limitation "and wherein, the first and second recombination DNA sequences direct *homologous recombination events between the first and second endogenous DNA sequences* in the genome of the mammalian cell upon introduction of the DNA construct into the mammalian cell, such that the first and second insertion DNA sequences are inserted into the genome of the mammalian cell between the first and second endogenous DNA sequences".

The newly added limitation to the claims filed on 09/15/2008 is unclear and contradicts to the existing limitation (A) because the new limitation requires, as written, *homologous recombination events between the first and second endogenous DNA sequences.* However, there is no limitation requiring sequence homology between the first and second endogenous DNA sequences that may result in the recited limitation "homologous recombination events between the first and second endogenous DNA sequences". Rather limitation (A) recites "wherein the first recombination DNA sequence is homologous to a first endogenous DNA sequence in the genome of a mammalian cell, and the second recombination DNA sequence is homologous to a second endogenous DNA sequence in the genome of the mammalian cell". Claims 72-75 depend from claim 71.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

New Matter

3. Claims 71-77 **remain** rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. *This is a new matter rejection*. 37 CFR 1.118 (a) states that "No amendment shall introduce **new matter** into the disclosure of an application after the filing date of the application". Applicant's arguments filed 09/15/2008 have been fully considered and they are not persuasive. Previous rejection is ***maintained*** for the reasons of record advanced on pages 5-8 of the office action mailed on 03/14/2008, and is revised below to address claim amendments filed on 09/15/2008.

In the instant case, the newly added limitation "the first and second recombination DNA sequences direct homologous recombination events between the first and second endogenous DNA sequences in the genome of the mammalian cell" recited in claims 71, 76, and 77 is considered as new matter. The specification does not disclose homologous recombination events between the first and second endogenous DNA sequences in the genome of the mammalian cell, wherein the events are directed by the DNA construct comprising the first and second recombination DNA sequences, as recited in claims 71, 76 and 77. Claims 72-75 depend from claim 71.

Applicants point to support for the amendments to the claims is found throughout the application as filed, such as at page 4, lines 1-13, which corresponds to paragraphs [0021]-[0023] of US 2004/0203153, publication of instant application, see recitation below.

[0021] The object of the invention is a process for specific replacement, in particular by targeting of a DNA, called *insertion DNA*, constituted by a part of a gene capable of being made

functional, or the function of which may be made more effective, when it is recombined with a complementing DNA in order thus to supply a complete recombinant gene in the genome of a eukaryotic cell, characterized in that:

[0022] the site of insertion is located in a selected gene, called the recipient gene, containing the complementing DNA and in that

[0023] eukaryotic cells are transfected with a vector containing an insert itself comprising the insertion DNA and two so-called "flanking" sequences on either side of the DNA of insertions, respectively homologous to two genomic sequences which are adjacent to the desired insertion site in the recipient gene,

There is no explicit recitation of the term "the first and second recombination DNA sequences direct homologous recombination events between the first and second endogenous DNA sequences in the genome of the mammalian cell" in the specification of instant application, nevertheless, the term appears to involve certain functionality of the DNA sequences. However, the limitation "the first and second recombination DNA sequences direct homologous recombination events between the first and second endogenous DNA sequences in the genome of the mammalian cell" does not appear to be art recognized with respect to basic scientific research and potential clinical application of homologous recombination. There is no written description regarding what are the "recombination DNA sequences" and Applicant's intention to define the term "recombination DNA sequences" by newly added limitation "the first and second recombination DNA sequences direct homologous recombination events between the first and second endogenous DNA sequences in the genome of the mammalian cell" has failed to clarify what the recited "recombination DNA sequences" are and what sequences have been recombined, as discussed in the maintained 71-77 rejected under 35 U.S.C. 112, second paragraph .

In the art, it has been shown that for a DNA sequence to be engaged in homologous recombination, the DNA sequence needs to be recognized by an enzyme, including a specialized endonuclease or topoisomerase-like enzyme, and a double strand DNA break in the DNA sequence is generated by the enzyme. For instance, **Chen et al.,** for instance, reviewed the mechanism gene conversion as one of the two mechanisms of homologous recombination. Chen et al. indicates that the mechanisms of gene conversion involve blunt-ended double-strand break and unidirectional transfer of genetic material from "donor" sequences to a highly homologous "acceptor" (See abstract, Figure 1, Chen et al., Gene conversion: mechanisms, evolution and human disease. *Nat Rev Genet.* 8(10):762-75, 2007). As an additional example, **Cromie et al.** discussed the characteristics of DNA molecules with resected (i.e. with cohesive end) double strand break (DSB) that are required for reciprocal DNA recombination events called crossover (CO) and non-crossover (NCO), and Cos and NCOs arise through different branches of the recombination pathway (See Cromie et al., Branching out: meiotic recombination and its regulation. *Trends Cell Biol.* 17(9):448-55, 2007). The specification does not describe what characteristics define a "recombination DNA sequence". Accordingly, in the absence of written description of the newly introduced term "recombination DNA sequence" recited in claims 71, 76 and 77, the claims as amended contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claims 72-75 depend from claim 71.

Applicants are reminded that it is their burden to show where the specification supports any amendments to the claims. See 37 CFR 1.121 (b)(2)(iii), the MPEP 714.02, 3rd paragraph,

last sentence and also the MPEP 2163.07, last sentence.

MPEP 2163.06 notes, "If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. *In re Rasmussen*, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)." MPEP 2163.02 teaches that "Whenever the issue arises, the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed...If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application. MPEP 2163.06 further notes "When an amendment is filed in reply to an objection or rejection based on 35 U.S.C. 112, first paragraph, and a study of the entire application is often necessary to determine whether or not "new matter" is involved. *Applicant should therefore specifically point out the support for any amendments made to the disclosure*.

Scope of enablement

4. Claims 71-77 are newly rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a DNA construct for homologous recombination, comprising: (A) a first flanking DNA sequence and a second flanking DNA sequence, wherein the first flanking DNA sequence is homologous to a first endogenous DNA sequence in the genome of a mammalian cell, and the second flanking DNA sequence is homologous to a second endogenous DNA sequence in the genome of the mammalian cell; and (B) a first insertion DNA

sequence and a second insertion DNA sequence, wherein the first insertion DNA sequence encodes a first gene product that does not confer resistance to a selection agent involved in the selection of transformants, the second insertion DNA sequence encodes a second gene product that confers resistance to a selection agent involved in the selection of transformants, the second insertion DNA sequence is downstream of the first insertion DNA sequence, the second insertion DNA sequence is operatively linked to regulatory elements that direct expression in transformed cells of the second gene product that confers resistance to the selection agent, and the first gene product is part or all of a receptor; wherein the first and second insertion DNA sequences are located between the first and second flanking DNA sequences in the DNA construct; and wherein upon introduction of the DNA construct into the mammalian cell, *the first flanking DNA sequences recombine with the homologous sequences of the first endogenous DNA sequences in the genome of the mammalian cell, and the second flanking DNA sequences recombine with the homologous sequences of the second endogenous DNA sequences in the genome of the mammalian cell*, such that the first and second insertion DNA sequences are inserted into the genome of the mammalian cell between the first and second endogenous DNA sequences, **does not** reasonably provide enablement for said DNA construct wherein *the first and second recombination DNA sequences direct homologous recombination events between the first and second endogenous DNA sequences in the genome of the mammalian cell* upon introduction of the DNA construct into the mammalian cell. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. *This rejection is necessitated by claim amendments filed on 09/15/2008.*

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

The nature of the instant invention is related to a procedure for specific replacement of a copy of a gene present in the genome of a recipient eukaryotic organism by the integration of a gene different from the inactivated gene (See paragraph [0001] of instant application). The breadth of the claims: claim 71 and its dependent claims 72-75 encompass any DNA construct harbors any two genes from any organism, wherein one of the gene confers resistance to a selection agent involved in the selection of transformants and other gene encodes a gene product is part or all of a receptor; claim 76 encompasses any DNA construct harbors any two genes from any organism, wherein one of the gene confers resistance to a selection agent involved in the selection of transformants and other gene encodes a gene product is part of all of an interferon; claim 77 encompasses any DNA construct harbors any two genes from any

organism, wherein one of the gene confers resistance to a selection agent involved in the selection of transformants and other gene encodes a gene product is part of all of an interleukin.

The specification discloses that the selection gene Neo^R, under the control of a promoter TK, was incorporated into the DNA to be inserted in order to make possible the selection of the transformants. The specification noted that the experiments described in the prior art implied a selection by means of the recipient gene (e.g. HPRT) or by means of the inserted gene (e.g. Neo^R) (See paragraph [0015] of instant application). The specification further indicates that, in the prior art, the exogenous sequences on the vector thus serve both to target the integration site and to introduce the modification. Subsequent to homologous recombination, the modified gene is always found in its normal genetic environment (See paragraph [0016] of instant application).

Consistent with the disclosure in the specification of instant application, in the art, **Mansour et al.** teaches a construct pINT-2LACZN/TK containing a lacZ gene positioned to create an in-frame fusion with the int-2 protein-coding region (See diagram below, Mansour et al., Introduction of a lacZ reporter gene into the mouse int-2 locus by homologous recombination. *Proc Natl Acad Sci U S A.* 87(19):7688-92, 1990; this reference has been cited on page 14 of the office action mailed on 03/14/2008).

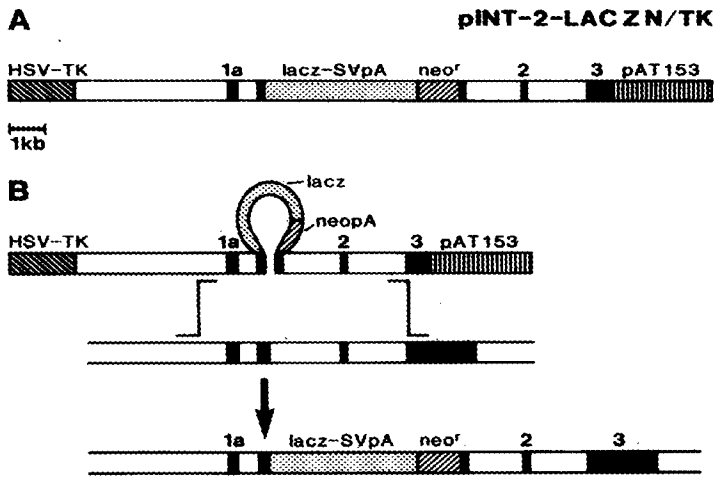

FIG. 3. *int-2–lacZ* targeting vector. (*A*) The closed boxes represent *int-2* exons (22, 23). Open boxes represent introns and noncoding sequences. The hatched boxes represent *neo*^{r} and HSV-tk DNAs as labeled, the stippled box denotes *lacZ* DNA, and the vertically striped box represents plasmid sequences. (*B*) Homologous recombination between the introduced vector DNA (pINT-2-LACZN/TK, upper line) and the endogenous *int-2* locus (middle line) gives rise to a mutant allele (lower line) in which *lacZ* sequences are fused in-frame with *int-2* coding sequences. Shadings are as described for *A*.

However, the newly added limitation in claim 71, 76, and 77 recites "wherein the first and second recombination DNA sequences direct *homologous recombination events between the first and second endogenous DNA sequences in the genome of the mammalian cell* upon introduction of the DNA construct into the mammalian cell", which contradict to the disclosure of specification and the status of art that teaches upon introduction of the DNA construct into the mammalian cell, *the first flanking DNA sequences recombine with the homologous sequences of the first endogenous DNA sequences in the genome of the mammalian cell, and the second flanking DNA sequences recombine with the homologous sequences of the second endogenous DNA sequences in the genome of the mammalian cell,* such that the first and second insertion DNA sequences are inserted into the genome of the mammalian cell between the first and second endogenous DNA sequences (See diagram above by Mansour et al., 1990). Accordingly, there is

lack of predictability of the DNA construct further limited by newly added limitation to perform the intended use disclosed in the specification regarding specific replacement of a copy of a gene present in the genome of a recipient eukaryotic organism by the integration of a gene different from the inactivated gene.

In view of the state of the art, the unpredictability in the art, and the lack of specific guidance and working examples in the specification, one of skill in the art would have to perform undue experimentation to make and use the claimed invention commensurate in scope with the claims 71-77.

Priority date of claims

The following information has been documented on pages 2-3 of the office action mailed on 06/06/2007.

The Non-Final office action mailed on 03/13/2007 noted that the applicants filed in the Oath or Declaration claiming priority dates of foreign applications FRANCE PCT/FR90/00185 03/19/1990 and FRANCE 89 03630 03/20/1989 in the instant application. The Examiner noted that the English translation of foreign applications FRANCE PCT/FR90/00185 03/19/1990 and FRANCE 89 03630 03/20/1989 has not been made of record in accordance with 37 CFR 1.55. See MPEP § 201.15.

In the response filed on 3/13/2007, Applicant indicated that on December 19, 1990, a certified translation of Application No. PCT/FR90/00185 was filed in Application No. 07/598,679, to which this application claims priority. Applicant further indicates that on June 11, 1998, a certified translation of Application No. FR 89 03630 was filed in Application No. 08/301,037, to which this application claims priority. As provided in M.P.E.P. 201.14(b)(11),

Applicant argues that no submission of further certified copies is required in the instant application and requests that the Office acknowledge that the required certified translations of the priority applications have been filed.

Applicant's clarification pertaining to certified translation of Application No. PCT/FR90/00185 and Application No. FR 89 03630 been filed during the prosecution of the Parent applications, 07/598,679 and 08/301,037, of instant application, was appreciated. Accordingly, Applicant has perfected the requirement under 37 CFR 1.55 for claiming the foreign priority. *Nevertheless, it is worth emphasizing that to claim the priority date, no new matter can be introduced.*

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

5. Claims 71 and 73 **remain** rejected under 35 U.S.C. 103(a) as being unpatentable over **Mansour et al.** (Mansour et al., Introduction of a lacZ reporter gene into the mouse int-2 locus by homologous recombination. *Proc Natl Acad Sci U S A*. 87(19):7688-92, 1990) in view of **Petkovich et al.** (Petkovich et al. A human retinoic acid receptor which belongs to the family of nuclear receptors. *Nature* 330(6147): 444-50, 1987). Applicant's arguments filed 09/15/2008 have been fully considered and they are not persuasive. Previous rejection is ***maintained*** for the reasons of record advanced on pages 13-16 of the office action mailed on 03/14/2008.

Applicant's arguments and response to Applicant's arguments

Applicant's arguments that the priority date of this application is March 20, 1989, and the United States filing date is March 19, 1990, have been fully considered and found not persuasive. The Examiner notes that the claims as amended introduced **new matter** as discussed above in this office action, and can not claim the indicated foreign priority dates 03/20/1989 (filing date of FRANCE 89 03630) or 03/19/1990 (filing date of FRANCE PCT/FR90/00185). Therefore, Mansour et al. published on October 1990 is qualified as a prior art.

Furthermore, The Examiner notes that the "recombination DNA sequence" recited in claims 71, 76, and 77 is interpreted as flanking sequences, as disclosed in paragraph [0023] of instant application. The newly added limitation "the first and second recombination DNA sequences direct homologous recombination events between the first and second endogenous DNA sequences in the genome of the mammalian cell" is interpreted as "the first flanking DNA

sequences recombine with the homologous sequences of the first endogenous DNA sequences in the genome of the mammalian cell, and the second flanking DNA sequences recombine with the homologous sequences of the second endogenous DNA sequences in the genome of the mammalian cell". Mansour et al. teaches these limitations as documented on pages 13-16 of the office action mailed on 03/14/2008

6. Claim 76 is rejected under 35 U.S.C. 103(a) as being unpatentable over **Mansour et al.** (Mansour et al., Introduction of a lacZ reporter gene into the mouse int-2 locus by homologous recombination. *Proc Natl Acad Sci U S A.* 87(19):7688-92, 1990) in view of **Chernajovsky et al.** (Chernajovsky et al., Efficient constitutive production of human fibroblast interferon by hamster cells transformed with the IFN-beta 1 gene fused to an SV40 early promoter. *DNA* 3(4): 297-308, 1984). Applicant's arguments filed 09/15/2008 have been fully considered and they are not persuasive. Previous rejection is ***maintained*** for the reasons of record advanced on pages 16-18 of the office action mailed on 03/14/2008.

Applicant's arguments and response to Applicant's arguments are the same as maintained rejection of claims 71 and 73 under 35 U.S.C. 103(a) as being unpatentable over Mansour et al. in view of Petkovich et al.

7. Claim 77 is rejected under 35 U.S.C. 103(a) as being unpatentable over **Mansour et al.** (Mansour et al., Introduction of a lacZ reporter gene into the mouse int-2 locus by homologous recombination. *Proc Natl Acad Sci U S A.* 87(19):7688-92, 1990) in view of **Lindenmaier et al.** (Lindenmaier et al., Isolation of a functional human interleukin 2 gene from a cosmid library by

recombination in vivo. *Gene* 39(1): 33-9, 1985). Applicant's arguments filed 09/15/2008 have been fully considered and they are not persuasive. Previous rejection is ***maintained*** for the reasons of record advanced on pages 18-20 of the office action mailed on 03/14/2008.

Applicant's arguments and response to Applicant's arguments are the same as maintained rejection of claims 71 and 73 under 35 U.S.C. 103(a) as being unpatentable over Mansour et al. in view of Petkovich et al.

8. Claims 71 and 74 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mansour et al. (Mansour et al., Introduction of a lacZ reporter gene into the mouse int-2 locus by homologous recombination. *Proc Natl Acad Sci U S A.* 87(19):7688-92, 1990) in view of Petkovich et al. (Petkovich et al. A human retinoic acid receptor which belongs to the family of nuclear receptors. *Nature* 330(6147): 444-50, 1987) as applied to claim rejection of claims 71 and 73 above, and further in view of **George et al.** (George et al., Receptor density and cAMP accumulation: analysis in CHO cells exhibiting stable expression of a cDNA that encodes the beta 2-adrenergic receptor. *Biochem Biophys Res Commun.* 150(2): 665-72, 1988) and **Emorine et al.** (Emorine et al., Molecular characterization of the human beta 3-adrenergic receptor. *Science* 245(4922): 1118-21, 1989). Applicant's arguments filed 09/15/2008 have been fully considered and they are not persuasive. Previous rejection is ***maintained*** for the reasons of record advanced on pages 20-21 of the office action mailed on 03/14/2008.

Applicant's arguments and response to Applicant's arguments are the same as maintained rejection of claims 71 and 73 under 35 U.S.C. 103(a) as being unpatentable over Mansour et al. in view of Petkovich et al.

9. Claims 71, 72 and 75 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mansour et al. (Mansour et al., Introduction of a lacZ reporter gene into the mouse int-2 locus by homologous recombination. *Proc Natl Acad Sci U S A.* 87(19):7688-92, 1990) in view of Petkovich et al. (Petkovich et al. A human retinoic acid receptor which belongs to the family of nuclear receptors. *Nature* 330(6147): 444-50, 1987) as applied to claim rejection of claims 71 and 73 above, and further in view of **Sleckman et al.** (Sleckman et al., Expression and function of CD4 in a murine T-cell hybridoma. *Nature* 328(6128): 351-3, 1987). Applicant's arguments filed 09/15/2008 have been fully considered and they are not persuasive. Previous rejection is ***maintained*** for the reasons of record advanced on pages 22-23 of the office action mailed on 03/14/2008.

Applicant's arguments and response to Applicant's arguments are the same as maintained rejection of claims 71 and 73 under 35 U.S.C. 103(a) as being unpatentable over Mansour et al. in view of Petkovich et al.

The following rejections under 35 U.S.C. 103(a) are necessitated by claim amendments filed by Applicant on 09/15/2008 based on the claim interpretations documented below.

Claim interpretations: The "recombination DNA sequence" recited in claims 71, 76, and 77 is interpreted as flanking sequences, as disclosed in paragraph [0023] of instant application. The newly added limitation "the first and second recombination DNA sequences direct homologous recombination events between the first and second endogenous DNA sequences in the genome of the mammalian cell" is interpreted as "the first flanking DNA sequences

recombine with the homologous sequences of the first endogenous DNA sequences in the genome of the mammalian cell, and the second flanking DNA sequences recombine with the homologous sequences of the second endogenous DNA sequences in the genome of the mammalian cell".

10. Claims 71 and 73 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over **Nandi et al.** (Nandi et al., Regulated expression of genes inserted at the human chromosomal beta-globin locus by homologous recombination. *Proc Natl Acad Sci U S A.* 85(11):3845-3849, 1988) in view of **Petkovich et al.** (Petkovich et al. A human retinoic acid receptor which belongs to the family of nuclear receptors. *Nature* 330(6147): 444-50, 1987). *This rejection is necessitated by claim amendments filed by Applicant on 09/15/2008.*

Nandi et al. teaches regulated expression of genes inserted at the human chromosomal beta-globin locus by homologous recombination by transfecting mammalian cells with a plasmid carrying a modified human beta-globin gene and a foreign gene composed of the coding sequence of the bacterial neomycin-resistance gene linked to simian virus 40 transcription signals (SV*neo*), and stable transformed cells were obtained in which the two genes are integrated at the beta-globin locus on human chromosome 11, and the genes inserted at the beta-globin locus were induced during differentiation (See abstract, and Figure 1(a), see diagram and legend below, Nandi et al., 1988).

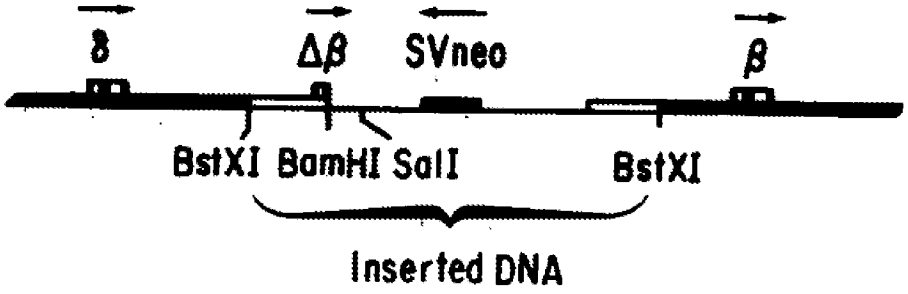

FIG. 1. (a) Structure of the modified human β-globin locus. The modification was produced by a homologous recombination between plasmid-derived human β-globin sequences (open bars) on pΔβ117 and resident human 13-globin sequences (solid bars) present in a Hu 11 MEL-human hybrid cell. The line indicates sequences mostly derived from pSV2neo, from which pΔβ117 was constructed. The position and direction of transcription of the globin (δ, Δβ, and β) and SV*neo* genes are indicated by the raised boxes and arrows.

Nandi et al. 1988 does not teach (i) the first gene (i.e. targeted locus in mammalian genome) product is part or all of a receptor, as recited in claim 71, and (ii) wherein the receptor is a retinoic acid receptor, as recited in claim 73 of instant application.

However, at the time the claimed invention was made, the cDNA clone encoding a retinoic acid receptor was known in the art. For instance, Petkovich et al. disclose a cDNA clone encoding a retinoic acid receptor that binds retinoic acid with high affinity (See abstract, Petkovich et al., 1987).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time of the invention to combine the teachings Nandi et al. 1988 regarding the gene targeting construct comprising a modified β-globin gene for altering the endogenous genomic copy of the β-globin gene locus, with the teachings of Petkovich et al. regarding a specific cDNA clone encoding retinoic acid receptor, to arrive at the claimed DNA construct of claims 71 and 73.

One having ordinary skill in the art would have been motivated to substitute the modified b-globin gene construct taught by Nandi et al. 1988 with the cDNA clone encoding retinoic acid receptor taught by Petkovich et al. in order to drive the expression of a retinoic acid receptor gene bearing an intended modification in target cells, thereby enabling the functional analysis of the retinoic acid receptor during differentiation and under different physiological conditions.

There would have been a reasonable expectation of success given (i) the construct taught by Nandi et al. 1988 can successfully alter gene of interest in a mammalian genome, and (ii) the construct for cDNA clone encoding retinoic acid receptor was readily available by the teachings of Petkovich et al.

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

11. Claim 76 is rejected under 35 U.S.C. 103(a) as being unpatentable over **Nandi et al.** (Nandi et al., Regulated expression of genes inserted at the human chromosomal beta-globin locus by homologous recombination. *Proc Natl Acad Sci U S A.* 85(11):3845-3849, 1988) in view of **Chernajovsky et al.** (Chernajovsky et al., Efficient constitutive production of human fibroblast interferon by hamster cells transformed with the IFN-beta 1 gene fused to an SV40 early promoter. *DNA* 3(4): 297-308, 1984). *This rejection is necessitated by claim amendments filed by Applicant on 09/15/2008.*

The teachings of Nandi et al., 1988 have been discussed in the preceding rejection of claims 71 and 73 under 35 U.S.C. 103(a) as being unpatentable over Nandi et al. (1988) in view of Petkovich et al. (1987).

Nandi et al. (1988) does not teach (i) the first gene (i.e. targeted locus in mammalian genome) product is part or all of an interferon, as recited in claim 76 of instant application.

However, at the time the claimed invention was made, the cDNA clone encoding an interferon was known in the art. For instance, Chernajovsky et al. teach the construction of the plasmid pSVEIF, which harbors the interferon β1 (INF- β1) gene (See Figure 1, Chernajovsky et al., 1984).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time of the invention to combine the teachings Nandi et al. 1988 regarding the gene targeting construct comprising a modified β-globin gene for altering the endogenous genomic copy of the β-globin gene locus, with the teachings of Chernajovsky et al. regarding a specific cDNA clone encoding interferon β1, to arrive at the claimed DNA construct of claim 76.

One having ordinary skill in the art would have been motivated to substitute the modified β-globin gene construct taught by Nandi et al. 1988 with the cDNA clone encoding interferon β1 taught by Chernajovsky et al. in order to drive the expression of interferon β1 gene bearing an intended modification in target cells, thereby enabling the functional analysis of the interferon β1 during differentiation and under different physiological conditions.

There would have been a reasonable expectation of success given (i) the construct taught by Nandi et al. 1988 can successfully alter gene of interest in a mammalian genome, and (ii) the construct for cDNA clone encoding interferon β1 was readily available by the teachings of Chernajovsky et al.

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

12. Claim 77 is rejected under 35 U.S.C. 103(a) as being unpatentable over **Nandi et al.** (Nandi et al., Regulated expression of genes inserted at the human chromosomal beta-globin locus by homologous recombination. *Proc Natl Acad Sci U S A.* 85(11):3845-3849, 1988) in view of **Lindenmaier et al.** (Lindenmaier et al., Isolation of a functional human interleukin 2 gene from a cosmid library by recombination in vivo. *Gene* 39(1): 33-9, 1985). *This rejection is necessitated by claim amendments filed by Applicant on 09/15/2008.*

The teachings of Nandi et al., 1988 have been discussed in the preceding rejection of claims 71 and 73 under 35 U.S.C. 103(a) as being unpatentable over Nandi et al. (1988) in view of Petkovich et al. (1987).

Nandi et al. (1988) does not teach (i) the first gene (i.e. targeted locus in mammalian genome) product is part or all of an interleukin, as recited in claim 77 of instant application.

However, at the time the claimed invention was made, the cDNA clone encoding an interleukin was known in the art. For instance, Lindenmaier et al. teach the construction of the plasmid pAN26-IL2, which harbors the interleukin 2 gene (IL2) (See Figure 1, Lindenmaier et al., 1985).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time of the invention to combine the teachings Nandi et al. 1988 regarding the gene targeting construct comprising a modified β-globin gene for altering the endogenous genomic copy of the β-globin gene locus, with the teachings of Lindenmaier et al. regarding a specific cDNA clone encoding interleukin 2 gene, to arrive at the claimed DNA construct of claim 77.

One having ordinary skill in the art would have been motivated to substitute the modified β-globin gene construct taught by Nandi et al. 1988 with the cDNA clone encoding in interleukin

2 gene taught by Lindenmaier et al. in order to drive the expression of interleukin 2 gene bearing an intended modification in target cells, thereby enabling the functional analysis of the interleukin 2 during differentiation and under different physiological conditions.

There would have been a reasonable expectation of success given (i) the construct taught by Nandi et al. 1988 can successfully alter gene of interest in a mammalian genome, and (ii) the construct for cDNA clone encoding interleukin 2 gene was readily available by the teachings of Lindenmaier et al.

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

13. Claims 71 and 74 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Nandi et al.** (Nandi et al., Regulated expression of genes inserted at the human chromosomal beta-globin locus by homologous recombination. *Proc Natl Acad Sci U S A.* 85(11):3845-3849, 1988) in view of **Petkovich et al.** (Petkovich et al. A human retinoic acid receptor which belongs to the family of nuclear receptors. *Nature* 330(6147): 444-50, 1987) as applied to claim rejection of claims 71 and 73 above, and further in view of **George et al.** (George et al., Receptor density and cAMP accumulation: analysis in CHO cells exhibiting stable expression of a cDNA that encodes the beta 2-adrenergic receptor. *Biochem Biophys Res Commun.* 150(2): 665-72, 1988) and **Emorine et al.** (Emorine et al., Molecular characterization of the human beta 3-adrenergic receptor. *Science* 245(4922): 1118-21, 1989). *This rejection is necessitated by claim amendments filed by Applicant on 09/15/2008.*

The teachings of Nandi et al. 1988 and Petkovich et al. 1987 have been discussed in the preceding rejection of claims 71 and 73 under 35 U.S.C. 103(a) as being unpatentable over Nandi et al. 1988 and Petkovich et al. 1987.

Nandi et al. 1988 and Petkovich et al 1987 do not teach the receptor is a 3-β adrenergic receptor, as recited in claim 74 of instant application.

However, at the time the claimed invention was made, the cDNA clone encoding a 3-β adrenergic receptor was known in the art. For instance, George et al. disclose a plasmid pUC13B2AR containing a beta 2-adrenergic receptor (See Material and Methods, page 666, George et al., 1988) and Emorine et al. teach that human beta 3-adrenergic receptor shares 45.5% identical amino acid sequences of human beta 2-adrenergic receptor.

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time of the invention to combine the teachings Nandi et al. 1988 regarding the gene targeting construct comprising a modified β-globin gene for altering the endogenous genomic copy of the β-globin gene locus, with the teachings of George et al. and Emorine et al. regarding a specific cDNA clone encoding a beta 3-adrenergic receptor, to arrive at the claimed DNA construct of claim 74.

One having ordinary skill in the art would have been motivated to substitute the modified β-globin gene construct taught by Nandi et al. 1988 with the cDNA clone encoding an beta 3-adrenergic receptor taught by George et al. and Emorine et al. in order to drive the expression of beta 3-adrenergic receptor gene bearing an intended modification in target cells, thereby enabling the functional analysis of the beta 3-adrenergic receptor during differentiation and under different physiological conditions.

There would have been a reasonable expectation of success given (i) the construct taught by Nandi et al. 1988 and Petkovich et al. 1987 can successfully alter gene of interest in a mammalian genome, including a retinoic acid receptor, and (ii) the construct for cDNA clone encoding a beta 3-adrenergic receptor was readily available by the combined teachings of George et al. and Emorine et al.

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

14. Claims 71, 72 and 75 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Nandi et al.** (Nandi et al., Regulated expression of genes inserted at the human chromosomal beta-globin locus by homologous recombination. *Proc Natl Acad Sci U S A.* 85(11):3845-3849, 1988) in view of **Petkovich et al.** (Petkovich et al. A human retinoic acid receptor which belongs to the family of nuclear receptors. *Nature* 330(6147): 444-50, 1987) as applied to claim rejection of claims 71 and 73 above, and further in view of **Sleckman et al.** (Sleckman et al., Expression and function of CD4 in a murine T-cell hybridoma. *Nature* 328(6128): 351-3, 1987). *This rejection is necessitated by claim amendments filed by Applicant on 09/15/2008.*

The teachings of Nandi et al., 1988 and Petkovich et al. 1987 have been discussed in the preceding rejection of claims 71 and 73 under 35 U.S.C. 103(a) as being unpatentable over Nandi et al., 1988 and Petkovich et al. 1987.

Nandi et al., 1988 and Petkovich et al. 1987 do not teach the receptor is a receptor for infectious agent recited in claim 72, and an HIV receptor recited in claim 75 of instant application.

However, at the time the claimed invention was made, the cDNA clone encoding a HIV receptor CD4 was known in the art. For instance, Sleckman et al. teach the retroviral vector construction MNST4, which harbors the CD4 gene (the receptor of infectious HIV) (See Figure 1, Sleckman et al., 1987). HIV is an infectious agent (as recited in claim 72) and the CD4 is a cellular receptor of HIV. Through interaction between which HIV envelope protein and CD4 receptor present on cell surface (an HIV receptor as recited in claim 75), the HIV can infect the cell.

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time of the invention to incorporate the teachings Nandi et al., 1988 and Petkovich et al. 1987, regarding the gene targeting construct comprising a modified β-globin gene for altering the endogenous genomic copy of the β-globin gene, with the teachings of Sleckman et al. regarding a specific cDNA clone encoding HIV receptor, to arrive at the claimed construct of claims 72 and 75.

One having ordinary skill in the art would have been motivated to incorporate the teachings of Nandi et al., 1988 and Petkovich et al. 1987 with the teachings of Sleckman et al. in order to drive the expression of a HIV receptor gene in target cells, thereby enabling the functional analysis of the HIV receptor during pathogenesis of AIDS and under different physiological conditions.

There would have been a reasonable expectation of success given (i) the construct taught by Nandi et al., 1988 and Petkovich et al. 1987 can successfully alter gene of interest in a mammalian genome, including a retinoic acid receptor, and (ii) the construct for cDNA clone encoding an HIV receptor CD4 was readily available by the teachings of Sleckman et al.

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

Obviousness-type double patenting rejection

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

15. Previous provisional rejection of claims 71-77 of instant application No. 10/770,418 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims

90, 99 and 108 of the other U.S. application of copending application No. 10/639,754, is ***withdrawn***.

It is noted that the Applicant did not address the provisional obviousness-type double patenting rejection in the response filed on 09/15/2008. However, the claims 90, 99 and 108 of the copending application No. 10/639,754 have been cancelled as of 03/06/2008. Newly added claims 117-153 of copending application No. 10/639,754 on 03/06/2008 are directed to methods (e.g. Claim 117 of copending application No. 10/639,754 is directed to a method of making a mouse embryo comprising cells having a genome comprising a recombinant heterologous gene), not directed to products (i.e. DNA constructs).

Conclusion

16. No claim is allowed.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Any inquiry concerning this communication from the examiner should be directed to Wu-Cheng Winston Shen whose telephone number is (571) 272-3157 and Fax number is 571-273-3157. The examiner can normally be reached on Monday through Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the supervisory patent

examiner, Peter Paras, Jr. can be reached on (571) 272-4517. The fax number for TC 1600 is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Wu-Cheng Winston Shen/

Patent Examiner
Art Unit 1632